Notice of Allowability	Application No.	Applicant(s)	
	09/878,686	SALE, MARK EDWARD	
	Examiner	Art Unit	
	Kandasamy Thangavelu	2123	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address--

All claims being allowable, PROSECUTION ON THE MERITS IS (OR REMAINS) CLOSED in this application. If not included herewith (or previously mailed), a Notice of Allowance (PTOL-85) or other appropriate communication will be mailed in due course. **THIS NOTICE OF ALLOWABILITY IS NOT A GRANT OF PATENT RIGHTS.** This application is subject to withdrawal from issue at the initiative of the Office or upon petition by the applicant. See 37 CFR 1.313 and MPEP 1308.

1. ☒ This communication is responsive to *March 21, 2005*.

2. ☒ The allowed claim(s) is/are *1,4-6,10-18,21-23 and 26*.

3. ☒ The drawings filed on *11 June 2001* are accepted by the Examiner.

4. ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
   a) ☐ All b) ☐ Some* c) ☐ None of the:
      1. ☐ Certified copies of the priority documents have been received.
      2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
      3. ☐ Copies of the certified copies of the priority documents have been received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

   * Certified copies not received: _____.

Applicant has THREE MONTHS FROM THE "MAILING DATE" of this communication to file a reply complying with the requirements noted below. Failure to timely comply will result in ABANDONMENT of this application.
THIS THREE-MONTH PERIOD IS NOT EXTENDABLE.

5. ☐ A SUBSTITUTE OATH OR DECLARATION must be submitted. Note the attached EXAMINER'S AMENDMENT or NOTICE OF INFORMAL PATENT APPLICATION (PTO-152) which gives reason(s) why the oath or declaration is deficient.

6. ☐ CORRECTED DRAWINGS (as "replacement sheets") must be submitted.
   (a) ☐ including changes required by the Notice of Draftsperson's Patent Drawing Review (PTO-948) attached
      1) ☐ hereto or 2) ☐ to Paper No./Mail Date _____.
   (b) ☐ including changes required by the attached Examiner's Amendment / Comment or in the Office action of Paper No./Mail Date _____.

Identifying indicia such as the application number (see 37 CFR 1.84(c)) should be written on the drawings in the front (not the back) of each sheet. Replacement sheet(s) should be labeled as such in the header according to 37 CFR 1.121(d).

7. ☐ DEPOSIT OF and/or INFORMATION about the deposit of BIOLOGICAL MATERIAL must be submitted. Note the attached Examiner's comment regarding REQUIREMENT FOR THE DEPOSIT OF BIOLOGICAL MATERIAL.

Attachment(s)

1. ☒ Notice of References Cited (PTO-892)
2. ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
3. ☐ Information Disclosure Statements (PTO-1449 or PTO/SB/08), Paper No./Mail Date _____
4. ☐ Examiner's Comment Regarding Requirement for Deposit of Biological Material
5. ☐ Notice of Informal Patent Application (PTO-152)
6. ☐ Interview Summary (PTO-413), Paper No./Mail Date _____ .
7. ☒ Examiner's Amendment/Comment
8. ☒ Examiner's Statement of Reasons for Allowance
9. ☒ Other *See note below*.

A Broda

SAMUEL BRODA, ESQ.
PRIMARY EXAMINER

Copies of references are not provided as they were submitted by the applicant as appendices to the specification.

DETAILED ACTION

Introduction

1. This communication is in response to the Applicant's communication dated March 21, 2005. Claims 1, 3-8, 15, 17-19, 21, 23 and 25-26 were amended. Claims 2 and 24 were canceled. Claims 27 and 28 were added. Claims 1, 3-23 and 25-28 of the application are pending.

Drawings

2. The drawings submitted on June 11, 2001 are accepted.

Examiner's Amendment

3. Authorization for this examiner's amendment was given in a telephone conversation by Mrs. Elaine Sale on June 1, 2005.

An examiner's amendment to the record appears below. Should the changes and/or additions be unacceptable to the applicant, an amendment may be filed as provided by 37 CFR 1.312. To ensure consideration of such an amendment, it MUST be submitted no later than the payment of the issue fee.

4. In the Specification:

4.1 Replace Page 2, Lines 1 to 11 with the following:

CROSS-REFERENCE TO PROVISIONAL APPLICATION

This application claims the benefit of Provisional Application Serial No. 60/210,672, filed 10 June 2000, entitled "Unsupervised Machine Learning-Based Mathematical Model Identification", the disclosure of which is hereby incorporated by reference in its entirety as if set forth fully herein.

FIELD OF THE INVENTION

The invention relates to methods, systems and computer program products that are used to identify optimal or near optimal mathematical models. In a preferred embodiment, the mathematical models describe pharmacological concentrations (pharmacokinetic models) or effects of drugs (pharmacodynamic models).

BACKGROUND OF THE INVENTION

Mathematical/statistical models are standard tools in determining how to best use drugs. Models are developed of the time course of the concentration of drugs (referred to as pharmacokinetic models) in various tissues, and the effects of drugs (referred to as

pharmacodynamic models). These models are then used to understand the most appropriate dose and dosing interval, as well as whether and how to adjust doses for special populations (elderly, pediatric, patients with various diseases). In addition, these models can be used to simulate a variety of clinical applications (e.g., treatment of different population, different algorithms for adjusting doses and evaluating patient responses), in order to evaluate clinical trial designs (clinical trial simulation) or clinical practice. The current method for identification of the mathematical model that best describes the data (the optimal model) is a complex process based on knowledge of the properties of the drug and trial and error. The current process is best described as a manual binary tree search using forward addition.

4.2 Replace Page 15, Lines 17-27 with the following:

minimizing an overall objective function, wherein the overall objective function is computed by combining –2 * log likelihood value with a penalty for each parameter estimated, a penalty for each element of the interindividual variance matrix estimated, a penalty for each element of the intraindividual variance matrix estimated, a penalty imposed if the minimization does not conclude successfully, a penalty if the standard errors of the parameter estimates cannot be obtained, a penalty if the correlation matrix of the estimates has any element > 0.95 and a "niche" penalty for being similar to other models in the population (within a "niche radius" of other models.

4.3 Replace Page 16, Lines 5 to 24 with the following:

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) optionally, scaling the overall objective function of each model to be between and upper limit R and a lower limit S wherein the ratio of R to S is between 2:1 and 100:1;

f) providing a number y of models to be in a subsequent generation;

g) selecting with replacement y number of parents of the said subsequent generation from the current generation, wherein the probability of selection of a model in the current generation is proportional to said fitness or optionally to said scaled fitness;

h) associating said parents into m groups comprising p parents where p is an integer greater than 1;

i) optionally, selecting some fraction of the m groups of parents to undergo at least one cross over;

j) optionally, crossing over said selected fraction at a random location on said bit string to create two new individuals for said subsequent generation;

k) assigning bit strings in current generation that are not selected for cross over to said subsequent generation;

l) optionally, randomly mutating bits of said subsequent generation bit strings wherein said mutation comprises changing a bit value 0 to a bit value of 1 or changing a bit value of 1 to a bit value of 0; and

m) repeating the steps of c through l until further decrease in the lowest value of the overall objective function (improvement in maximum fitness) no longer occurs.

4.4 Replace page 18, Lines 4 to 23 with the following:

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model and optionally representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) searching the candidate search space using simulated annealing, wherein simulated annealing comprises the steps of:

i) randomly selecting one model from the candidate set of models;

ii) selecting an initial value for temperature (T) wherein T represents the tolerance of a minimization process for retaining a model that results in a higher energy; and T is defined as a change in value of the overall objective function;

iii) assessing the energy of the initial model, wherein energy is defined as the value of the overall objective function;

iv) randomly changing the model to generate a subsequent model;

v) assessing the energy of the subsequent model using the methods of steps c) and d) above;

vi) retaining the subsequent model as the current model if the energy is lower than the current model;

vii) if the energy of the subsequent model is higher than the energy of the current model, computing the probability of retaining it as:

$$e^{\Delta E/KT}$$

where T is the temperature, ΔE is the change in energy (current model energy - subsequent model energy), and k is Boltzman's constant; or

Otherwise, rejecting the subsequent model;

viii) reducing the value of T;

ix) randomly selecting one model from the candidate set of models; and

x) repeating the steps of iv through ix until further reduction in energy (overall objective function) no longer occurs.

4.5 Replace Page 19, Line 13 to Page 20, Line 1 with the following:

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model and optionally representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) initializing the search with a call to OCL setup in the OptQuest callable library and initialize a population of models with a call to OCLInitpop;

f) initializing each search dimension with a call to OCLdefinevar in the OptQuest callable library;

g) selecting an initial model from the candidate search space using scatter search/path relinking and tabu search as implemented in the OptQuest Callable library from OptTek systems by calling the function Octretsolution;

h) searching the candidate search space using Scatter search/path relinlking/Tabu search using the OptQuest Callable library wherein Scatter search/path relinking/Tabu search comprises the steps of:

i) evaluating the overall objective function of the current model;

ii) adding the value of the overall objective function of the current model to the OptQuest Callable library database with a call to the function OCL putSolution;

iii) finding the overall objective function of the best model thus far evaluated with a call to the function OCLGetBest in the OptQuest Callable Library;

iv) getting the subsequent model with a call to the function OCLGetSolution; and

v) repeating steps i-iv until either the required number of evaluations or convergence is seen; and

i) deleting current problem from memory with a call to OCLGoodBye.

4.6 Replace Page 28, Lines 18 to 20 with the following:

The calculation of the overall objective function is:

Overall objective function = fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for

4.7 Replace Page 29, Line 27 to Page 30, Line 14 with the following:

When the overall objective functions are calculated, it is often helpful, if they are scaled. The upper and lower limits of the scaled overall objective functions are defined by the user.

Common values are 3 (for upper) and 0.2 (for lower). This is done to improve the numerical stability of the model. In this application, linear regression is performed between the points

(mean of overall objective function-2 sd of overall objective function, lower limit of overall objective function)

and

(mean of overall objective function+2 sd of overall objective function, upper limit of overall objective function)

and the unscaled overall objective function values linearly transformed by this linear relationship. Value greater than or less than the mean +/-2 standard deviations are assigned the upper or lower limit of overall objective function, respectively. The scaling process prevents very large or very small values of overall objective function from driving the selection.

From these scaled overall objective function values, a new generation of individuals (models) is created. Note that, contrary to the usual definition of fitness in genetic algorithm, a lower value is better in this application (lower value for -2 log likelihood corresponds to a higher likelihood of the data, given the parameters). In the scaling process, this relationship is reversed, so that a more fit individual is assigned a higher fitness, and therefore a higher probability of entering into the next generation gene pool. Individuals from the old generation are randomly selected, with replacement to enter into the next generation gene pool. The probability of selection is proportional to the scaled fitness.

4.8 Replace Page 31, Lines 9-10 with the following:

This completes the creation of the next generation of models. This process is repeated until further decrease in the lowest value of the overall objective function (improvement in maximum fitness) no longer occurs.

4.9 Replace Page 38, Lines 23 to 26 with the following:

This is applied to the search for an optimal model as follows: An initial random model is created. An initial high temperature is defined. The "energy" is calculated. The energy in simulated annealing is same as the overall objective function in genetic algorithm. We want to minimize the overall objective function (the energy) and maximize the fitness. The temperature is defined as change in the overall objective function that is acceptable. A random change is

5. In the claims:

5.1 Replace amended claim 1 with the following:

1. A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) searching said models using the objective functions and a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter search/path relinking, neural networks, tabu search and genetic algorithm to select the next set of models;

f) repeating steps c) to e) with the selected method of searching and next set of models until no further improvement in the lowest value of overall objective functions of models is achieved;

g) selecting the model with lowest value of the objective function as the optimal or near optimal model.

5.2 Delete claim 3.

5.3 Replace amended claim 4 with the following:

4. The method of claim 1, wherein the NONMEM/NMTRAN control files are generated for each model selected in step b) or step e) by substituting text associated with each selected feature into a control file template;

the NONMEM/NMTRAN is run using the said control files; and

the computed goodness of fit (fitness) is input to an overall objective function generator to compute the overall objective function in step d).

5.4 Replace amended claim 5 with the following:

5. The method of claim 1, wherein the overall objective function is computed by combining –2 * log likelihood value with a penalty for each parameter estimated, a penalty for each element of the interindividual variance matrix estimated, a penalty for each element of the intraindividual variance matrix estimated, a penalty imposed if the minimization does not conclude successfully, a penalty if the standard errors of the parameter estimates cannot be obtained, a penalty if the correlation matrix of the estimates has any element > 0.95 and a

"niche" penalty for being similar to other models in the population (within a "niche radius" of other models.

5.5 Replace amended claim 6 with the following:

6. A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is

the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) optionally, scaling the overall objective function of each model to be between and upper limit R and a lower limit S wherein the ratio of R to S is between 2:1 and 100:1;

f) providing a number y of models to be in a subsequent generation;

g) selecting with replacement y number of parents of the said subsequent generation from the current generation, wherein the probability of selection of a model in the current generation is proportional to said fitness or optionally to said scaled fitness;

h) associating said parents into m groups comprising p parents where p is an integer greater than 1;

i) optionally, selecting some fraction of the m groups of parents to undergo at least one cross over;

j) optionally, crossing over said selected fraction at a random location on said bit string to create two new individuals for said subsequent generation;

k) assigning bit strings in current generation that are not selected for cross over to said subsequent generation;

l) optionally, randomly mutating bits of said subsequent generation bit strings wherein said mutation comprises changing a bit value 0 to a bit value of 1 or changing a bit value of 1 to a bit value of 0; and

m) repeating the steps of c through l until further decrease in the lowest value of the overall objective function (improvement in maximum fitness) no longer occurs.

5.6 Delete claims 7, 8 and 9.

5.7 Replace amended claim 17 with the following:

17. A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty.

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) searching the candidate search space using simulated annealing, wherein simulated annealing comprises the steps of:

i) randomly selecting one model from the candidate set of models;

ii) selecting an initial value for temperature (T) wherein T represents the tolerance of a minimization process for retaining a model that results in a higher energy; and T is defined as a change in value of the overall objective function;

iii) assessing the energy of the initial model, wherein energy is defined as the value of the overall objective function;

iv) randomly changing the model to generate a subsequent model;

v) assessing the energy of the subsequent model using the methods of steps c) and d) above;

vi) retaining the subsequent model as the current model if the energy is lower than the current model;

vii) if the energy of the subsequent model is higher than the energy of the current model, computing the probability of retaining it as:

$$e^{\Delta E/KT}$$

where T is the temperature, ΔE is the change in energy (current model energy - subsequent model energy), and k is Boatman's constant; or

Otherwise, rejecting the subsequent model;

viii) reducing the value of T;

ix) randomly selecting one model from the candidate set of models; and

x) repeating the steps of iv through ix until further reduction in energy (overall objective function) no longer occurs.

5.8 Delete claims 19 and 20.

5.9 Replace amended claim 21 with the following:

21. A computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models, comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) initializing the search with a call to OCL setup in the OptQuest callable library and initialize a population of models with a call to OCLInitpop;

f) initializing each search dimension with a call to OCLdefinevar in the OptQuest callable library;

g) selecting an initial model from the candidate search space using scatter search/path relinking and tabu search as implemented in the OptQuest Callable library from OptTek systems by calling the function Octretsolution;

h) searching the candidate search space using Scatter search/path relinlking/Tabu search using the OptQuest Callable library wherein Scatter search/path relinking/Tabu search comprises the steps of:

i) evaluating the overall objective function of the current model;

ii) adding the value of the overall objective function of the current model to the OptQuest Callable library database with a call to the function OCL putSolution;

iii) finding the overall objective function of the best model thus far evaluated with a call to the function OCLGetBest in the OptQuest Callable Library;

iv) getting the subsequent model with a call to the function OCLGetSolution; and

v) repeating steps i-iv until either the required number of evaluations or convergence is seen; and

i) deleting current problem from memory with a call to OCLGoodBye.

5.10 Replace amended claim 23 with the following:

23. A computer program product comprising computer usable storage medium having computer executable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model from a set of candidate models, the process comprising:

a) defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) searching said models using the objective functions and a method selected from the group consisting of: full grid search, simulated annealing, integer programming, scatter

search/path relinking, neural networks, tabu search and genetic algorithm to select the next set of models;

f) repeating steps c) to e) with the selected method of searching and next set of models until no further improvement in the lowest value of overall objective functions of models is achieved;

g) selecting the model with lowest value of the objective function as the optimal or near optimal model.

5.11 Delete claim 25.

5.12 Replace amended claim 26 with the following:

26. A computer program product comprising computer usable storage medium having computer executable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model from a set of candidate models, the process comprising:

a) defining a candidate search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model;

b) selecting an initial set of candidate models by selecting one feature from each set of mutually excusive features by a uniform random process for each candidate model and representing each model by a bit string;

c) computing a goodness of fit (fitness) of each model in terms of the log likelihood using a pharmacokinetic and/or pharmacodynamic model;

d) calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model,), theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95;

e) optionally, scaling the overall objective function of each model to be between and upper limit R and a lower limit S wherein the ratio of R to S is between 2:1 and 100:1;

f) providing a number y of models to be in a subsequent generation;

g) selecting with replacement y number of parents of the said subsequent generation from the current generation, wherein the probability of selection of a model in the current generation is proportional to said fitness or optionally to said scaled fitness;

h) associating said parents into m groups comprising p parents where p is an integer greater than 1;

i) optionally, selecting some fraction of the m groups of parents to undergo at least one cross over;

j) optionally, crossing over said selected fraction at a random location on said bit string to create two new individuals for said subsequent generation;

k) assigning bit strings in current generation that are not selected for cross over to said subsequent generation;

l) optionally, randomly mutating bits of said subsequent generation bit strings wherein said mutation comprises changing a bit value 0 to a bit value of 1 or changing a bit value of 1 to a bit value of 0; and

m) repeating the steps of c through l until further decrease in the lowest value of the overall objective function (improvement in maximum fitness) no longer occurs.

5.13 Delete claims 27 and 28.

Reasons for Allowance

6. Claims 1, 4-6, 10-18, 21-23 and 26 of the application are allowed over prior art of record.

7. The following is an Examiner's statement of reasons for the indication of allowable subject matter:

The closest prior art of record shows:

(1) a method and apparatus for determining in a biological material, one or more unknown values of certain material, using a model based on a set of samples and a multivariate algorithm using wavelength subsets; the model's fitness is determined by a fitness function based on performance and cost; the method uses a genetic algorithm to search the space of possible wavelength subsets; the initial population of wavelengths is selected randomly and represented by bit strings; the fitness of each member of the population is evaluated; and weak individuals are eliminated; then new population is created by mating and reproduction and mutation; through iteration of this procedure, the genetic algorithm eventually converges to a wavelength subsets that have high fitness (**Thomas et al.,** U. S. Patent 5,857,462);

(2) a method and an apparatus for segmenting an image in which an arbitrarily shaped contour is deformed stochastically until it approximates the contour of the target object; the evolution of the contour is controlled by a simulated annealing process which causes the contour to settle into a global minimum of an image-derived energy function; the energy function is derived from the statistical properties of the previously generated images; the initial contour is selected by a random process; the contour is allowed to evolve through a series of local perturbations; deformations that lowered the system's energy were always accepted thus providing for consistent downhill moves; in addition, occasional uphill moves were accepted, to prevent the system from being stuck in local minima; after a large number of moves were evaluated at a given temperature, the temperature was decreased by a modest amount; the cooling system tended to converge to the global energy minimum (**Levin et al.,** U. S. Patent 5,768,413);

(3) construction, training and use of neural networks for optimization of the administration of drugs; numerous factors influence the clinical effects of medication; neural networks are used to estimate the optimal dosage of one or more drugs for a particular patient; the neural network based drug dosage estimator combines a number of variables influencing drug response into a single empirical computer model; the model uses three groups of parameters – those related to the individual's description, those related to medical diagnostic indications and those related to pharmacological indications (Pharmacokinetic and pharmacodynamic indicators); the neural network is trained with training data from historical medical records; one of the neural networks that performs the best on the training data is used as selected model (**Tang et al.,** U. S. Patent 6,658,396); and

(4) variability of pharmacokinetic and pharmacodynamic (PK-PD) parameters across patients; NONMEM is a widely used program for pharmacokinetic and pharmacodynamic population analysis; NONMEM describes the interindividual variability in terms of fixed and random effects; for finding a population model, it is necessary to find the covariates that significantly affect the PK-PD parameters; data analysis is performed using a stepwise approach; first Bayes estimates of PK parameters are obtained; then the relationship between the individual PK parameter estimates and the covariates is modeled using a generalized additive model (GAM) to allow non-linear covariate parameter relationships to be discovered; finally, the population model is built using NONMEM on the basis of the GAM analysis (**Mandema et al.,** "Pharmacometrics", Journal of Pharmacokinetics and Biopharmaceutics, Vol. 20, No. 5, 1992).

7.1 Applicant's first set of claims consists of Claims 1, 4 and 5.

Independent Claim 1 is directed to a computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models. The claim identifies the uniquely distinct features of:

"defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model" and "calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95".

Because the closest prior art fails to teach or fairly suggest defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is

chosen from each set of mutually exclusive features for each candidate model; and calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95, as claimed by the Applicant, Claims 1, 4 and 5 are deemed novel and allowable.

7.2 Applicant's second set of claims consists of Claims 6 and 10-16.

Independent Claim 6 is directed to a computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models. The claim identifies the uniquely distinct features of:

"defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for

each candidate model" and "calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95".

Because the closest prior art fails to teach or fairly suggest defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is

the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95, as claimed by the Applicant, Claims 6 and 10-16 are deemed novel and allowable.

7.3 Applicant's third set of claims consists of Claims 17-18.

Independent Claim 17 is directed to a computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models. The claim identifies the uniquely distinct features of:

"defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model" and "calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is

the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95".

Because the closest prior art fails to teach or fairly suggest defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95, as claimed by the Applicant, Claims 17-18 are deemed novel and allowable.

7.4 Applicant's fourth set of claims consists of Claims 21 and 22.

Independent Claim 21 is directed to a computer implemented method for selecting a near optimal or optimal mathematical model from a set of candidate models. The claim identifies the uniquely distinct features of:

"defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model" and "calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95".

Because the closest prior art fails to teach or fairly suggest defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95, as claimed by the Applicant, Claims 21 and 22 are deemed novel and allowable.

7.5 Applicant's fifth set of claims consists of Claim 23.

Independent Claim 23 is directed to computer program product comprising computer usable storage medium having computer executable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model from a set of candidate models. The claim identifies the uniquely distinct features of:

"defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model" and "calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95".

Because the closest prior art fails to teach or fairly suggest defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95, as claimed by the Applicant, Claim 23 is deemed novel and allowable.

7.6 Applicant's sixth set of claims consists of Claim 26.

Independent Claim 26 is directed to a computer program product comprising computer usable storage medium having computer executable instructions which when executed on a computer perform a process for selecting a near optimal or optimal mathematical model from a set of candidate models. The claim identifies the uniquely distinct features of:

"defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model" and "calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not, success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95".

Because the closest prior art fails to teach or fairly suggest defining a candidate model search space having n dimensions, wherein n is a positive integer and each dimension represents a set of mutually exclusive features from which exactly one of said mutually exclusive features is chosen from each set of mutually exclusive features for each candidate model; and calculating for each model an overall objective function given by the expression:

fitness + theta penalty • ntheta + random effect penalty • nrand + success • success penalty + covariance • covariance penalty + correlation • correlation penalty,

wherein fitness is –2 * log likelihood of the observed data given a pharmacokinetic and/or pharmacodynamic model, theta penalty is the penalty for each fitted parameter, ntheta is the number of parameters, random effect penalty is the penalty for each random effect, nrand is the number of random effects, success is 0 if the minimization was successful and 1 if not,

success penalty is the penalty if the minimization is not successful, covariance is 0 if the covariance step was successful and 1 if not, covariance penalty is the penalty if the covariance step is not successful, correlation is 0 if no estimation correlations are > 0.95 and 1 if at least one is > 0.95 and correlation penalty is the penalty for a correlation > 0.95, as claimed by the Applicant, Claim 26 is deemed novel and allowable.

8. Any comments considered necessary by applicant must be submitted no later than the payment of the issue fee and, to avoid processing delays, should preferably accompany the issue fee. Such submissions should be clearly labeled "Comments on Statement of Reasons for Allowance."

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Dr. Kandasamy Thangavelu whose telephone number is 571-272-3717. The examiner can normally be reached on Monday through Friday from 8:00 AM to 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kevin Teska, can be reached on 571-272-3716. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to TC 2100 Group receptionist: 571-272-2100.

K. Thangavelu
Art Unit 2123
June 1, 2005

SAMUEL BRODA, ESQ.
PRIMARY EXAMINER